REMARKS

Claims 1-13 *and* 25-33 were pending in the application. Claims 25-29.32 *and* 33 are withdrawn from consideration. Claims 1-13, 30 and 31 were examined and rejected. Claims 5.12 *and* 13 were also objected to. Applicants have amended most of the claims. Some of these amendments are directed to typographical errors and other informalities as discussed below.

Claims 5 and 30 are newly cancelled, and new claims 34-38 are added. Therefore, claims 1-4, 6-13, 31, and 34-38 are now active.

Most importantly, Claim 1 has been amended to incorporate the limitations of claim 30 in large part, with several key exceptions. ***Not*** included in amended claim 1 is a "molecule or agent that induces or upregulates expression of a Hedgehog protein". This embodiment is no longer present in any of the pending claims. Also excluded from claim 1 is the language (in prior claim 30) "active homologue or variant" of the Hedgehog protein (whether referring to the polypeptide, the encoding nucleic acid construct, or transformed bacterial or animal cell embodiments). This language has also been deleted from any claims in which it previously occurred. In accordance with the importation of language from claim 30 into claim 1, claim 30 has been cancelled.

Amended claim 1 is limited in structural terms to polypeptides that share at least 63% sequence identity to one of three sequences (SEQ ID NO:1, 2 or 3) (or to a nucleic acid expressing the polypeptide or a cell expressing it). In addition to the foregoing limitation, the scope of the polypeptide (and therefore, nucleic acid/cell) embodiments of claim 1 is further narrowed by a set of functional limitations. Thus, in the claimed method, the polypeptide:

(i) binds to a Hedgehog binding receptor Patched, and can activate signaling downstream of Patched though the receptor Smoothened and the Gli family of transcriptional effectors;

(ii) acts to maintain homeostasis of {adult} intestinal epithelium;

(iii) restores *epithelial* differentiation of GI tract cells to avoid carcinogenesis; and/or

(iv) causes gastric and/or colonic epithelial tumorigenic cells to undergo a cell death program and avoid carcinogenesis, promoting their shedding into the GI lumen.

The description of such functional activities are found throughout the specification, for example, page 3, lines 1-7; and page 5, lines 6-14; page 7, lines 7-9; page 8, lines 30-31, and page 54, lines 7-11

The dependency of a number of dependent claims has been amended to refer to claim 1 instead of cancelled claim 30.

Claims 2 and 8 are amended to narrow "cancer of the GI tract" to cancer of the small intestine and colon. As a result, claim 5 is viewed as superfluous and is cancelled.

Claims 8 and 9 are amended to refer to "the source of Hedgehog protein" of claim 1, without reciting, unnecessarily, the four different "sources" now present in claim 1. This also serves to remove the prior "homologue or variant" language of these claims as well as any reference to an agent or molecule that induces/upregulates Hh protein.

New claim 34, further characterizes the activity of the polypeptide recited in claim 1 with respect to additional downstream receptor binding and action through certain transcription effectors. This is supported at several places in the specification, for example, at page 35, line 14, through page 36, line 6 and the cited drawings.

New claims 35-38 narrow the polypeptide of claim 1 to increasing degrees of sequence identity to three reference SEQ ID NO's. Support in the specification is at page 4, lines 21-23 and page 4, line 31 – page 5, line 2.

No new matter is being introduced by these amendments and their entry is respectfully requested. In view of the amendments, new claims and the remarks that follow, applicants believe that the claims are now in condition for allowance and earnestly solicit their passage to issue.

I. Withdrawal of Requirement for Election of Species

Applicants acknowledge and thank the examiner for reconsideration and withdrawal of the requirement to make two species elections, namely (1) to one species of a "source of a Hedgehog protein, and (2) to a single species of cancer. The claims are believed to have been examined without limitation to either of the previously elected species.

II. Objections to the Specification

The specification was objected to on two separate grounds of informality.

A. *Priority Statement*

The Office required a priority statement to be included in the first sentence of the specification or application data sheet. The specification is amended herein to comply with this requirement.

B. *Embedded Hyperlink*

The specification was objected to because it contains an embedded hyperlink at page 15, line 32. This hyperlink has been removed by the present amendment.

III. Formal Objections to Claims

Claims 5, 12 and 13 were objected to because of

- an extraneous space between the final word of claim 5 and the period; and .
- each of claims 12 and 13 contain an extraneous space after the number "30" in the recitation of the dependency

These typographical errors in claims and 12 and 13 have been corrected, and claim 5 has been cancelled, rendering these objections moot.

IV. REJECTIONS UNDER 35 USC § 112, 2nd PARAGRAPH (Indefiniteness)

All pending claims (1-13, 30 and 31) are rejected as being indefinite.

A. "Deficient"

The term **"deficient"** in claim 1 is said to be a relative term which renders the claim indefinite. The term "deficient" is allegedly not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree (of deficiency). A person of ordinary skill in the art allegedly would not be reasonably apprised of the scope of the invention. For example, the Action notes that Shh protein is undetectable in adult human colon, but is detectable in adult human stomach (citing to page 34, lines 1-14). The Action contends that it is unclear whether or not this would be considered "a deficiency" in a Hedgehog protein.

Applicants Response:

Applicants respectfully disagree with this rejection for the following reasons. The specification provides definitional support for the term "deficiency" as it refers to a Hedgehog protein. For example, see, page 8, lines 4-8, of the specification:

> The deficiency of the Hedgehog protein preferably is an acquired deficiency of the Hedgehog protein. The acquired deficiency of the Hedgehog protein in the GI tract may be the result of an acquired somatic mutation resulting in reduced expression of Hedgehog and/or a somatic mutation activating mutation in the Wnt-β-catenin pathway."

In addition at page 8, line 24 – page 9 line 8, the specification explains that the methods of the invention are intended to "maintain or restore" functional physiological levels of Hedgehog protein.

> In these prophylactic and therapeutic methods, the source of Hedgehog protein is administered in such an amount that functional levels of Hedgehog protein is maintained or restored in the subject's GI tract. The functional level of Hedgehog protein achieves the desired prophylactic or therapeutic effects. Such a functional level preferably is a level that maintains homeostasis of gastric and/or colonic epithelia, or a level that restores differentiation of tumorigenic cells in these tissues, more preferably a level that causes such intestinal cancerous cells to enter the Death program, allowing them to finally be shed into the lumen of the GI tract. … The norm for a functional level in a given intestinal

> tissue in a given physiological condition may be established by determining the Hedgehog proteins levels in the corresponding tissues under comparable conditions in healthy individuals by methods known in the art … the administered amount of the source of the Hedgehog protein may be therapeutic amount that effects a supranormal level of the Hedgehog protein in GI tract. Such a supranormal level may be a factor 1.5, 2, 3, 5, 10 or higher than the norm for a functional level of Hedgehog protein in GI tract.

It is understood from the foregoing what is meant by "deficiency," particularly with respect to what it means to overcome the deficiency. The functional limitations now present in claim 1, taken in part from the paragraph cited above, by explaining what they are activating, maintaining, restoring, and causing, effectively contribute to clarifying the meaning of "deficient" or "deficiency."

> A proper analysis of claims under the second paragraph of § 112:
>
> is merely to determine whether the claims do, in fact, set out and circumscribe a particular area with a reasonable degree of precision and particularity. It is here where the definiteness of the language employed must be analyzed-- not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art.

In re Moore, 169 USPQ 236, 238 (CCPA 1971). Applicants believe that in the present claims, the terms "deficiency" and "deficient" meet this standard. Therefore, this ground for rejection may properly be withdrawn.

B. *Use of Acronym "GI"*

Claim 1 is allegedly indefinite by its use of the **acronym "GI"** without being stated in full the first time it appears in the claims.

This ground for rejection is moot in view of the amendment of claim 1.

C. *"Active"*

Claim 30 is allegedly indefinite because the language "active homologue or variant" is unclear as to whether "active" applies to "homologue" alone or both "homologue and variant".

This ground for rejection is now moot in view of the amendment of claim 1 and various other dependent claims in which this language formerly appeared.

D. *"Shh" and "Ihh"*

Claim 31 is allegedly indefinite for reciting the acronyms "*Shh*" and "*Ihh*" without indicating at least once what these terms mean.

This ground for rejection is now moot in view of the amendment to claim 31.

V. REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH (Enablement)[1]

All pending claims were rejected as failing to comply with the enablement requirement.

The Office Action provided a *Wands* analysis of the claims, approximately as follows. The *nature of the invention* was defined by the Office as a method of treating a deficiency of a hedgehog protein in the gastrointestinal (GI) tract comprising administering a composition that comprises a source of a Hedgehog protein.

The Action noted that the specification provides two supporting working examples (pg 34-40), directed to "colonic tissues" (Example 1) and "gastric tissues" (Example 2). As discussed in the Action:

> Example 1.1: expression of Sonic (*Shh)* and Indian (I*hh*) hedgehog mRNA and protein in the colon; only *Ihh* protein was detectable in the adult colon.
>
> Example 1.3: *Ihh* staining "was completely lost" in adenomatous polyps and "was lost" in 8 of 9 carcinomas; *Ihh* expression already occurred at the polyp stage (page 36).
>
> Example 1.4: either butyrate or recombinant *Shh* protein (which has a "higher biological activity" than recombinant *Ih*") induced villin expression in colon cancer cell line HT-29, (a marker indicating restoration of differentiation).
>
> Example 1.5: butyrate induction of HT-29 (above) was blocked by the hedgehog pathway inhibitor, cyclopamine.
>
> Example 2.1: along the human GI tract, *Shh* protein was found only in the "fundic glands of the stomach" (page 38).
>
> Example 2.2: *Shh* protein expression was lost in areas of intestinal metaplasia which is a risk factor for development of gastric adenocarcinoma (page 38).
>
> Example 2.3: aberrant development of intestinal epithelium into gastric epithelium in fundic glands was accompanied by *Shh* expression.
>
> Example 2.4: in patients with Barrett's esophagus, the switch in differentiation from squamous to gastric epithelial tissue in fundic glands was accompanied by induction of *Shh* expression.

The Office Action notes that Examples 2.3 and 2.4 deal with aberrant Hedgehog protein expression, rather than "a deficiency of Hedgehog protein in the GI tract." This led the Office to conclude that these "do not relate to the claimed invention." According to the Office Action, "none of the working examples demonstrate treatment of a deficiency in a Hedgehog protein in a subject."

Applicant's Response Concerning "Deficiency

A broader definition of "deficiency" than that apparently considered by the Office is found at page 8, lines 4-8, of the specification (cited above in the discussion of the §112/2nd paragraph rejection. In addition at page 8, line 24 - page 9, line 8 (cited above, but repeated

[1] In this and the subsequent sections, Applicants responses and remarks appear either as sections labeled with headers "Applicants' Response…" , or as interspersed, shorter comments that are indented, italicized and in Arial font to help distinguish them from the description of the rejections.

below with emphasis added), the specification explains that the methods of the invention "maintain or restore" functional physiological levels of Hedgehog protein, (including the attainment of "supranormal" levels):

> In these prophylactic and therapeutic methods, the source of Hedgehog protein is administered in such an amount that functional levels of Hedgehog protein is maintained or restored in the subject's GI tract. The functional level of Hedgehog protein achieves the desired prophylactic or therapeutic effects. Such a functional level preferably is a *level that maintains homeostasis* of gastric and/or colonic epithelia, or a level that *restores differentiation of tumorigenic cells* in these tissues, more preferably a level that *causes such intestinal cancerous cells to enter the Death program*, allowing them to finally be shed into the lumen of the GI tract. … The norm for a functional level in a given intestinal tissue in a given physiological condition may be established by determining the Hedgehog proteins levels in the corresponding tissues under comparable conditions in healthy individuals by methods known in the art … the administered amount of the source of the Hedgehog protein may be therapeutic amount that ***effects a supranormal level*** of the Hedgehog protein in GI tract. Such a supranormal level may be a factor 1.5, 2, 3, 5, 10 or higher than the norm for a functional level of Hedgehog protein in GI tract.

Applicants contend that based on the foregoing disclosure combined with the Examples, this basis for the rejection should be withdrawn.

Role of Hedgehog Proteins is Allegedly Inadequately Understood in the Art

The Office takes that position that the role of hedgehog proteins in the adult human gastrointestinal tract is complex and not well understood, citing a review paper by one of the present inventors (van den Brink (2007) *Physiol Rev. 87*:1343-75). The Action cites or refers to selected passages of this publication as supporting its position, *e.g.:*

- "the relevance of the loss of Hedgehog signaling in colorectal carcinogenesis is not yet clear";
- it remains possible that the loss of Hedgehog signaling in the early stages of distal colon carcinogenesis is "an epiphenomenon" rather than playing "a causal role";
- different studies have provided conflicting results as to whether or not hedgehog signaling is active in colorectal cancer cells;
- "at later stages of carcinogenesis there is a gain of Hedgehog signaling that maintains viability of carcinoma cells;" and
- "[t]he spectacular effect of SMO inhibition on the viability of many gastrointestinal cancer cell lines suggests that the Hedgehog pathway may be an attractive target for cancer therapy."

The Action contrasts the teaching in the application that butyrate induces expression of Ihh in colon cancer cells, to statements in the prior art that the ability of butyrate administration to treat colon cancer is controversial - - citing Lupton *et al.*, 2004, for its statement at page 479, that

> [b]utyrate, an SCFA (small chain fatty acid) fiber fermentation product, is thought to be chemopreventative by some, but not all studies show this beneficial effect against colon cancer development

Lupton is also cited for its mention that, in one study, administration of butyrate "actually increased the percentage of rats with tumors" (at page 480). Other references are cited for disclosure that single chain fatty acids (SCFA) (including butyrate) did not alter proliferation in familial adenomatous polyposis (FAP) and that FAP patients are refractory to SCFA (Tonelli *et al.*, 1995)

The Office concludes from the foregoing that the skilled artisan could not predict whether administration of a Hedgehog protein (*e.g.*, Indian) to a subject with a deficiency in a Hedgehog protein (*e.g.,* lack of Ihh in a colon cancer) would (i) treat the deficiency, (ii) have no effect, or (iii) instead stimulate the hedgehog pathway stimulating cancer growth. The Office contends that undue experimentation would be required to test subjects with such deficiencies to determine the effectiveness of such treatment.

Applicants note that the ground for rejection based on the use of Hedgehog inducers such as butyrate are no longer applicable to the present claims that do not read on such methods. Moreover, the specification provides an adequate basis for the use of the indicated sources of Hedgehog proteins to achieve the objectives of the claimed methods.

Scope of the Claims is Allegedly Very Broad

The Office states that with respect to the deficiency to be treated, the nature of the treatment and the source of the administered Hedgehog protein, the broadest claims include treating deficiency of any Hedgehog protein (*e.g.*, Shh, Dhh, Ihh or variants) in any part of the GI tract (which the Office reads as encompassing the oral cavity, tongue, salivary glands, pharynx, esophagus, stomach, ileum, colon, cecum, appendix, rectum and anus) as well as associated organs (including the liver, gallbladder and pancreas).

As noted by the Office, specifically embodiments are gastric cancer (including carcinomas), colon cancer (including carcinomas), FAP), colonic adenomatous polyps, invasive adenocarcinomas, small intestinal adenomas and cancers and desmoid tumors.

The Office states that the claims encompass treatment of either adult or developing (*e.g.* , embryonic) subjects with a GI tract hedgehog deficiency.

Applicants note that they have amended claim 1 to state that the treatment is of an adult subject. This is intended to distinguish from the possibility that a developing embryo is being treated. Accordingly, the term adult is not intended to exclude pediatric subjects, who, while not adults from the

standpoint of aging or maturation, are nevertheless completely distinct from developing embryos.

The Office contends that the specification only provides two examples of a Hedgehog protein deficiency in the GI tract: loss of *Ihh* in the colon (adenomatous polyps and adenocarcinomas) and loss of *Shh* in intestinal metaplasia of the fundus. The Office concluded that these two limited examples do not enable the full range of potential GI tract ailments encompassed by the claims. The Office regards Applicants' disclosure that *Shh* is expressed in fundic gland heterotopia of the small intestine and fundic gland metaplasia of the esophagus as teaching that a lack of *Shh* expression is not common to all ailments of the GI tract. Rather, the Office contends, it would require undue experimentation to test all of possible GI tract ailments to determine "which if any are associated with a Hedgehog deficiency."

The Action also alleges that, while claims 3 and 5 recite the species of "gastric cancer," *no evidence exists of Hedgehog protein loss in gastric cancer* (stating further that fundic intestinal metaplasia is not a form of gastric cancer). For reasons, not understood by applicants, the Action then notes that the above-cited van den Brink (2007) reference reports (at pages1367-1368) that

> "cancer cell lines derived from the esophagus, stomach, pancreas and biliary tract showed high autonomous Hedgehog pathway activity. This was supported by the demonstration that PCT1 mRNA expression was highly induced in gastric and pancreatic carcinomas compared with adjacent normal tissue."

Applicants note that they have limited claims directed to treatment or prevention of particularly types of cancer (claim 2 and its dependent claims) to cancer of the small intestine and colon, so the claims no longer read on gastric cancer.

The Action focuses next on the term **"treating"** in the claims which is said to encompass not only therapy of patients suffering from a Hedgehog deficiency (*e.g.,* patients with cancer resulting from such deficiency) but also **preventing** of such diseases occurring in patients who are **"at risk"**. The Office contends that the claims would require the ability to diagnose "at risk" patients, and to prevent occurrence of disease in them. Thus, it was concluded that the alleged lack of enablement for therapeutic (*e.g.* for cancer) extends to lack of enablement for preventing the diseases.

Applicants note that exemplary support for "preventing" is provided in the form of the van Den Brink Declaration which describes after-filing experiments that confirm what was stated in the application regarding prevention of cancer

development. Specific language directed to "at risk" subjects has been deleted. The results presented in the Declaration show that Shh protein expressed in, and released from transgenic enteric bacterial cells are biologically active, and that delivery of these bacteria to the G. I. tract by oral gavage results in regionally selective expression of the Shh protein in mice. This expression is associated with prevention of the development of adenomatous polyps which are recognized precursors of GI cancer.

The Action then comments that the treatment methods comprise administration of compositions that include a "genus of variant sources of a Hedgehog protein" that include "a Hedgehog protein or "an **active homologue or variant thereof,**" nucleic acid vectors, enteric bacteria and animal cells encoding the proteins; and an agent that induces/upregulates Hedgehog protein expression. The Action describes Claims 1-7 as being generic to this genus of "sources", while claims 7, 8, 9, 30 and 31 encompass each type of source as a Markush-type group. Claims 10, 11, 12 and 13 each limit the source to one particular subgenus, *i.e.,* variant Hedgehog polypeptides (claims 10 and 11), nucleic acid vectors encoding variant Hedgehog polypeptides (claim 12) and enteric bacterium encoding variant Hedgehog polypeptides (claim 13).

These claims allegedly do not provide any limitation on the amount of variation permitted in Hedgehog homologues or variants, except for the recitation in claim 30 of "active homologue or variant". Moreover, the Office adds that it is not clear in claim 30 whether "active" applies to both homologue and variant in claim 30 (referring to the Indefiniteness rejections herein).

Applicants note that all instances of "homologue or variant" have been deleted from the claims.

The specification teaches that "[t]he term "Hedgehog" as used herein thus comprises polypeptides preferably having at least 63% amino acid identity with the amino acid sequence of SEQ ID NO:1 [human Desert hedgehog], SEQ ID NO:2 [human Indian hedgehog], SEQ ID NO:3 [human Sonic hedgehog]... " (page 4, line lines 19-21).

The Office asserts that because the term **"preferably"** was used, the claims encompass variants are *not limited* to those with at least 63% identity. As such, the claims encompass method of using a genus of variant Hedgehog polypeptides (and related nucleic acids and cells) that is highly variant because a significant number of structural differences between genus members are permitted.

Applicants respond that the scope of the polypeptides in the method of claim 1 (and its dependent claims) is now limited to those with at least 63% sequence identity to three specific sequences. Thus the scope of this claim has been substantially narrowed.

The Action continues that the claims do not require that the variant polypeptides possess any particular conserved structure or function, or other disclosed distinguishing feature. The claims only require the claimed polypeptides share some structural similarity to the isolated polypeptide of SEQ ID NO:1, 2, or 3. Thus, the claims are drawn to a genus of polypeptides defined *only* by sequence similarity. None of the claims include the limitation that the polypeptide variants exhibit characteristics of the parent polypeptide of SEQ ID NO:1, 2 or 3. Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to SEQ ID NO:1, 2 or 3 and variants thereof. If a variant of the protein is to have a structure and function similar to the protein corresponding to SEQ ID NO:1, 2 or 3, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein. Conversely, if a protein variant of SEQ ID NO:1, 2 or 3 need not have a disclosed property; the specification has failed to teach how to use such a variant.

Applicants respond that the scope of the polypeptides in the method of claim 1 (and its dependent claims) is now further limited beyond the structural (sequence) limitations by a set of four functional limitations that have been discussed above.

The Office Action went through a lengthy discussion of the problem of predicting protein structure from sequence data and in turn the complexity of utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex.

Applicants will not restate the details of the Office's analysis here but reiterate that they have imposed functional limitations on the claims (claim 1) a priori rather than ascertaining function from predicted structural criteria.

Applicants have allegedly provided little or no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change, *etc.*, and the nature and extent of changes that can be made. The specification's outline of art-recognized procedures for producing variants, is not considered adequate guidance.

References were cited by the Office for the proposition that the art recognizes that function cannot be predicted from structure alone.

Furthermore, claims 1-9, 11-13, 30 and 31 each are said to encompass treatment by administration of a nucleic acid that encodes a Hedgehog protein "or homologue or variant thereof" which is also considered to lack enablement because the specification does not disclose methods or working examples that indicate the claimed nucleic acid is introduced to an organism by administration and expressed in a cell for therapeutic purposes. The disclosure in the specification is, according to the Office merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

For example, the specification does not teach (i) vectors to introduce the claimed nucleic acid into the cell, or (ii) in what quantity or for what duration to administer them. The Office cites literature that is said to teach that since 1990, about 3500 patients have been treated by gene therapy, and despite some evidence of gene transfer, it has generally been inadequate in achieving a meaningful clinical response. Also noted in the Office Action is the major challenge associated with delivery of DNA to target tissues and transport to the cell nucleus to enable expression of the desired protein. Therefore, undue experimentation would be required introduce and express the claimed nucleic acid into the cell of an organism to treat a disease.

The Action states that gene therapy is unpredictable and complex because one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell. Due to the large quantity of experimentation necessary to express the claimed nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples, the complex nature of the invention, the state of the prior art that establishes the unpredictability of making transgenic animals and of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required.

Applicants believe that the art is replete with teachings of expression vectors of various types (plasmid, bacterial, viral, liposomes, etc.) that result in either transient or stable, constitutive or inducible protein expression in vivo after administering the vectors. Therefore, it is within the skill of the art to use the claimed nucleic acid embodiments as "sources of the Hedgehog polypeptides" to

achieve objectives of the claimed methods without undue experimentation or further inventive effort.

A similar conclusion was reached for the claimed treatment with a genus of molecules or agents that induce or upregulate expression of Hedgehog protein in a subject is also not enabled for the same reasons as above. Allegedly, the only exemplified compound is butyrate, used in Example 1.4 to induce Ihh expression in the colon cancer cell line HT-29. There is no limitation of "agent or molecule" as to structure, and this language would encompass proteins, nucleic acids, lipids, carbohydrates, small organic molecules, large organic molecules and more. It would require undue experimentation to make and test the large genus of potential molecules.

Applicants Additional Remarks Traversing the Lack of Enablement Rejection

The scope of the polypeptides in the method of claim 1 (and its dependent claims) is now limited to those with at least 63% sequence identity to three specific sequences. This scope carries over into the other three sources of Hedgehog protein (nucleic acid expression vectors, transformed bacterial cells or animal cells that express/secrete the polypeptide). Thus the scope of this claim has been substantially narrowed vs. the prior claims. Several new claims (35-38) further narrow the sequences of the polypeptide to 75, 80, 90 or 95% sequence identity to one of three reference sequences.

Claim 1 (and its dependent claims) now has a set of functional limitations that further limit the scope of the genus of polypeptides. This was discussed above. By combining a set of structural limitations based on sequence, even without specific discussion of segments of the polypeptide which can be modified, *etc.*, with significant functional limitations, Applicants believe that using methods known in the art and those disclosed herein, it would require no more than ordinary, routine experimentation to evaluate a given polypeptide for its utility in accordance with these claims as well as its "status" as falling inside or outside the claims' scope. Such experimentation, while not trivial, is not undue, and requires no inventive effort on the part of a skilled artisan. Moreover, the embodiment of agents/molecules that induce/upregulate Hedgehog protein have now been deleted from the claims.

Applicants respectfully point out that

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. [citations omitted] The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed....

In re Jackson, 217 USPQ 804, 807 (Bd. App. 1982, cited with approval in *Wands*, 8 USPQ2d at 1404).

Even when "unpredictability" in a field such as chemistry may create reasonable doubt as to the accuracy of a broad statement supporting enablement, and even when the statement is, on its face, contrary to generally accepted scientific principles, the Court of Customs and Patent Appeals (predecessor to the Federal Circuit), has clearly articulated that

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with a contested statement.

In re Marzocchi, 169 USPQ 367, 369 (CCPA 1967).

Applicants contend that the Office's *Wands* analysis and other evaluation of the prior claims would not be applicable to the claims as presently amended. Therefore it would be proper to withdraw the rejection for lack of enablement.

VI. REJECTIONS UNDER 35 USC § 112, 1st PARAGRAPH (Written Description)

All pending claims were rejected as failing to comply with the written description requirement. The claims allegedly contain subject matter which was not adequately described in the specification. As noted in the Action analysis of written description requires **understanding what Applicants are claiming and what Applicants "have possession of."**

This rejection tracks quite closely to the "lack of enablement" rejection above. As stated, the *(presumably meaning "some")* claims are genus claims encompassing methods of treatment with compositions comprising a genus of "variant sources" of a Hedgehog protein. This genus of sources is said to include

- a Hedgehog protein or an active homologue or variant thereof;
- nucleic acid vectors encoding said proteins;
- enteric bacteria encoding said proteins;
- animal cells encoding said proteins;
- a molecule or agent that induces or upregulates expression of Hedgehog protein.

According to the Office, the specification does adequately describe (relating to the language of claim 1) a method of treating Hedgehog protein deficiency in the GI tract of a subject deficient in the protein and in need of such treatment by administering one of the:

(a) the polypeptide of SEQ ID NO:1, 2 or 3, or
(b) butyrate.

Applicants' interject here their disagreement with the Office's conclusion that claim 1 should be limited as noted above in order to comply with the written description requirement, as characterized above. Rather applicants believe that the specification supports Applicants contention that it would be recognized by those of skill in the art that they were in possession of a somewhat broader genus of polypeptides (as well as encoding nucleic acid vectors, and bacterial or animal cells expressing the polypeptides) that includes those with at least 63% sequence identity to SEQ ID NO:1, 2 and 3 (as opposed to only 100% identity) ***AND*** *the functional attributes recited in amended claim 1.*

The Action characterizes the scope of the claims exactly the same way as in the enablement analysis above. These claims allegedly do not provide any limitation on the amount of variation permitted in Hedgehog homologues or variants, except for the recitation in claim 30 of "**active** homologue or variant". Moreover, the Office adds that it is not clear in claim 30 whether "active" applies to both homologue and variant in claim 30 (referring to the Indefiniteness rejection discussed above).

The Office Action characterizes Applicants' disclosure as follows:

> "[t]he term "Hedgehog" as used herein thus comprises polypeptides preferably having at least 63% amino acid identity with the amino acid sequence of SEQ ID NO:1 [human Desert hedgehog], SEQ ID NO:2 [human Indian hedgehog], SEQ ID NO:3 [human Sonic hedgehog]..."

(citing 5to pg 4, line lines 19-21). According to the Action, use of the term "preferably" indicates that encompassed variants are not necessarily limited to those with at least 63% identity. As such, the claims encompass use of a "highly variant" genus of Hedgehog polypeptides (or nucleic acid vectors, or cells). The Action alleges that the claims do not require that the variant polypeptides possess any particular conserved structure or function or other distinguishing feature. The claims only require the claimed polypeptides share "some structural similarity to the isolated polypeptide of SEQ ID NO:1, 2, or 3", so that sequence similarity is the only definition of the genus.

As to the genus of molecules/gents that induce/upregulate Hedgehog protein expression, the only exemplified molecule is butyrate (Example 1.4) which induces Ihh expression in the colon cancer cell line HT-29. The Action points out that the term "agent or molecule" as used in the claim is not limited by any structure, and therefore potentially encompasses any sort of protein, nucleic acid, lipid, carbohydrate, small organic molecule, large organic molecule, *etc.*

The Action states that the written description requirement for a claimed genus may be satisfied through

> sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The present specification allegedly fails to provide sufficient descriptive information (*e.g.*, , definitive structural or functional features, or critical conserved regions, of the genus of polypeptides, nucleic acids, cells, molecules or agents). There is allegedly no identification of any particular portion of the structure that must be conserved nor what changes should be made, the sites at which variability may be tolerated or the relation of structure to function.

The Office contends that the general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is needed. The prior art allegedly does not provide the missing structural disclosure or teaching of or correlations sufficient to **enable** one of skill to identify or isolate the polypeptides or nucleic acids encompassed by these claims.

Applicants note that the Office seems to be discussing "enablement" based on the bolded term above, not written description.

The Office asserts that one of skill could not predictably identify the encompassed molecules as being identical to those claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification is said not to provide adequate written description of the claimed genus. The Office asserts further that one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus leading to a conclusion that Applicants were not in possession of the claimed genus (citing *Vas-Cath Inc. v. Mahurkar*). The Office asserts that the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception has not been achieved until reduction to practice has occurred (citing further to *Fiers v. Revel,* (CAFC 1993), *Amgen Inc. v. Chugai Pharmaceutical* Co. *Ltd.,* 18 USPQ2d 1016 (CAFC 1991); and *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483 (Bd. Pat Appeals, Interfer. 1993).

Applicants Response

Applicants' remarks above in response to the rejection for lack of enablement apply here as well.

The scope of the polypeptides in the method of claim 1 (and its dependent claims) is now limited to those with at least 63% sequence identity to three specific sequences. Thus the scope of this claim has been substantially narrowed. Claim 1 also has a list of functional limitations that further limit the scope of the genus of polypeptides. With this combined set of structural limitations based on sequence, even without specific discussion of segments of the polypeptide which can be modified, *etc.*, together with significant functional limitations, Applicants believe that a person skilled in the art would recognize that at the time the application was filed, they were in possession of the invention claimed in the present claim set.

The function of the Written Description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material. *In re Smith*.178 USPQ 620 (CCPA 1973). It is not necessary that the application describe the claim limitations exactly. *In re Lukach* 169 USPQ 795 (C.C.P.A. 1971), but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations. *In re Smythe*. 178 USPQ 279,284 (C.C.P.A. 1973). Thus, the test is whether the disclosure of the application relied upon reasonably conveys to a person skilled in the art that the inventor had possession of the claimed subject matter at the time of the earlier filing date. *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985). "Precisely how close the original description must come to comply with the description requirement of §112 must be determined on a case-by-case basis." *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991)

As discussed by the court in *In re Wertheim,* the description requirement does not require that specification describe the claim limitations exactly, but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that Applicant's invention includes those limitations. The burden of showing that the claimed invention is not described in the specification rests on the PTO in the first instance, and it is up to the PTO to give reasons why a description not *in ipsis verbis* is insufficient. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976)

Applicants contend that the Office's analysis as applied to the earlier claims would not meet the burden for a *prima facie* case of inadequate written description imposed on the Office with respect to the amended claims. Therefore it would be proper to withdraw the rejections based on these grounds.

VII. REJECTIONS UNDER - 35 USC § 102(b) – LACK OF NOVELTY

Claims 1, 6-9, 30 and 31 were rejected as being anticipated by Tonelli *et al.*, 1995 (*Dis Colon Rectum 38*: 974-8) (hereinafter, "Tonelli").

First off, the Office Action focused on the preamble of claim 1, stating that the "intended use" would not lend patentable weight to the claim (beyond limiting the claim to treating a subject with a Hedgehog protein deficiency). The Action notes that a subject with FAP "inherently" meets this limitation of claim 1 (deficiency in Ihh in adenomatous polyps), citing a publication by present co-inventor Van den Brink and colleagues (*Nature Genetics. 36*:277-82 (2004) which Applicants note was after the present priority date. Therefore, a subject with FAP allegedly meets one limitation of claim 1 -- that the subject have a deficiency of a Hedgehog protein.

> *Applicants note that the Office appears to have understood without difficulty the meaning of "deficiency" when making this rejection…even while contending elsewhere that this term is indefinite.)*

As interpreted by the Office, the language "source of a Hedgehog protein" recited in claim 1 encompasses "a molecule or agent that induces or upregulates expression of Hedgehog protein in said subject". Both the specification and "relevant art" teach that butyrate inherently upregulates expression of Ihh (citing the same 2004 paper as above). Therefore, the Office concluded that the method of claim 1 encompasses a method of administering butyrate to a subject with FAP.

Tonelli allegedly teaches such a method (citing to the Abstract). Thus, it was concluded that Tonelli anticipates claim 1 as well as claims 6-9, 30 and 31 because these dependent claims read on the same method as discussed above.

Applicants Response

The amendments to claim 1 and various dependent claims no longer read on the use of "a molecule or agent that induces or upregulates expression of Hedgehog protein in said subject". The amended claims specifically enumerate four type of "sources" of a Hedgehog protein" to the exclusion of butyrate and other agents that induce or upregulate Hedgehog proteins. The claims are therefore clearly distinct from the disclosure in the Tonelli reference, which is no longer applicable to the pending claims. It would therefore be proper to withdraw this ground for rejection.

VIII. CONCLUSION

Applicants respectfully request entry of the amended and new claims, and the foregoing remarks. For reasons advanced above, the application is now believed to be in condition for allowance, which Applicants earnestly solicit.

Respectfully submitted,

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